Adjunctive brexpiprazole 1 mg and 2 mg daily for Japanese patients with major depressive disorder following inadequate response to antidepressants: a phase 2/3, randomized, double-blind (BLESS) study

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Aims: Inadequate antidepressant response interrupts effective treatment of major depressive disorder (MDD). The BLESS study evaluates the dosage, efficacy, and safety of brexpiprazole adjunctive therapy in Japanese patients with inadequate antidepressant therapy (ADT) response.

Methods: This placebo-controlled, randomized, multicenter, parallel-group phase 2/3 study randomized Japanese MDD patients (Hamilton Rating Scale for Depression 17-item total score ≥ 14; historical inadequate response to 1–3 ADTs) with inadequate response to 8-week single-blind, prospective SSRI/SNRI treatment to 6-week adjunctive treatment with brexpiprazole 1 mg, 2 mg, or placebo. The primary endpoint was change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline. Secondary endpoints included MADRS response, remission rate, and Clinical Global Impression-Improvement score. Safety was comprehensively evaluated, especially regarding antipsychotic adverse events (AEs).

Results: Of 1194 screened patients, 740 were randomized and 736 (1 mg, $n = 248$; 2 mg, $n = 245$; placebo, $n = 243$) had ≥1 baseline/post-baseline MADRS total score. The LSM (SE) change from baseline in MADRS total score at Week 6 by MMRM analysis was −8.5 (0.47) with brexpiprazole 1 mg, −8.2 (0.47) with brexpiprazole 2 mg, and −6.7 (0.47) with placebo (placebo-adjusted LSM difference [95% CI]: 1 mg, −1.7 [−3.0, −0.4]; $P = 0.0089$; 2 mg, −1.4 [−2.7, −0.1]; $P = 0.0312$). Secondary efficacy results supported the primary endpoint. Brexpiprazole was generally well tolerated.

Conclusion: Brexpiprazole 1 mg daily was an appropriate starting dose and both 1 mg and 2 mg daily were effective and well tolerated as adjunctive therapy for Japanese MDD patients not adequately responsive to ADT.

Keywords: *adjunctive therapy, antipsychotic, brexpiprazole, Japanese, major depressive disorder.*

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Major depressive disorder (MDD), a chronic, recurrent psychiatric disorder, causes significant morbidity and mortality related to suicide risk.[1] In Japan, the 12-month prevalence of MDD (males, 2.2%; females, 3.2%)[2] is lower than the global prevalence compared with other high-income countries.[3] Despite this, MDD is associated with enormous social and economic costs in Japan, mainly because of reduced workplace productivity and completed suicide.[4]

MDD treatment guidelines from the Japanese Society of Mood Disorders (JSMD)[5] are consistent with international guidelines and recommend first-line antidepressant therapy with one of the following agents: selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), or mirtazapine, a noradrenergic and specific serotonergic antidepressant. However, treatment responses are inadequate with antidepressant monotherapy in up to approximately 50% of patients and appear to decrease with further antidepressant treatment lines.[6] Lack of remission leads to ongoing disruption of well-being, social functioning, quality of life, and broader social and economic effects.[7,8] In cases of inadequate response, the JSMD guidelines suggest adjunctive therapy if improvement to dose increase or switching is only partial in terms of the spectrum of depressive symptoms or degree of improvement.[5]

Among the options for adjunctive therapy, atypical antipsychotics are associated with the highest evidence levels and are the only option approved by the United States Food and Drug Administration.[9,10] In Japan, aripiprazole is currently the only antipsychotic agent approved as adjunctive therapy for MDD. The efficacy of

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aripiprazole has been confirmed in a Japanese double-blind, placebo-controlled trial and international double-blind trials.[11,12] However, results of these trials suggest that a relatively high proportion of patients experience disruptive adverse events (AEs), especially akathisia and insomnia, which may prevent treatment for depressed patients with anxiety and insomnia symptoms. This limitation of aripiprazole justifies the need for other adjunctive therapy options. Patients also report troublesome subjective experiences, especially insomnia, anxiety, and fatigue[13] and addressing these would be of benefit.

Brexpiprazole is a serotonin–dopamine activity modulator that is a partial agonist at the serotonin 5-HT_{1A} and dopamine D_2 receptors and an antagonist at the serotonin 5-HT_{2A} and noradrenaline $\alpha_{1B/2C}$ receptors, all at similar potency.[14] Unlike aripiprazole, brexpiprazole exhibits subnanomolar potency against the above receptors meaning more potent actions at these receptors.[14] These partial agonist ($5\text{-HT}_{1A}/D_2$) and antagonist (5-HT_{2A}, $\alpha_{1B/2C}$) receptor activities modulate the serotonergic, noradrenergic, and dopaminergic systems and are thought to be associated with the antipsychotic and antidepressant effects of brexpiprazole. Further, optimal D_2 receptor intrinsic activity (i.e., less partial agonist activity) and potent serotonergic system effects are expected to lower the incidence and severity of akathisia and insomnia compared with aripiprazole.[15,16]

Brexpiprazole has been approved for the treatment of schizophrenia and MDD in over 60 countries since its first approval in the US in 2015.[17] Internationally, the brexpiprazole clinical trial program for adjunctive treatment in MDD has been robust and comprehensive, including four short-term trials (Pyxis,[18] Polaris,[19] Syrius,[20] Delphinus[21]) primarily focused on efficacy. International phase 3 studies have consistently shown a reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) total score following adjunctive brexpiprazole therapy at doses of 2 mg and 3 mg daily, the recommended approved target and maximum doses, respectively, in the US.[18–21] A lower incidence of akathisia and insomnia has been reported with brexpiprazole as adjunctive therapy compared with aripiprazole,[16] and is expected to

overcome these limitations of aripiprazole. This is believed to be one of the key advantages of brexpiprazole, which may also help improve long-term adherence.[22,23]

In Japan, brexpiprazole has been approved for the treatment of schizophrenia since January 2018 based on results of a 6-week randomized, double-blind, placebo-controlled trial in patients with acute relapse, as well as a 52-week long-term trial in outpatients.[24,25] Brexpiprazole pharmacokinetics are similar between Japanese and non-Japanese populations.[26] Therefore, brexpiprazole 2 mg daily used in clinical studies outside of Japan and approved in the US should also be effective and tolerable in Japanese patients with MDD. Brexpiprazole 1 mg daily was also chosen to confirm whether it is the lowest effective dose in Japanese patients, although this dose has not been validated in clinical studies in patients with MDD overseas.[19] In short-term overseas trials, the starting dose was 0.5 mg/day or 1 mg/day, but there was no significant difference in the incidence of adverse events during the titration period with either starting dose.[18–21] Therefore, a starting dose of 1 mg daily was set, with the objectives of reaching an effective dose quickly, and corroborating if a 1 mg starting dose would represent an effective and tolerable dose in Japanese patients. On this background, the BLESS study aimed to evaluate the efficacy and tolerability of brexpiprazole at doses of 1 mg and 2 mg daily as adjunctive therapy to antidepressant therapies (ADTs) compared with adjunctive placebo, in patients with MDD who showed an inadequate response to antidepressant monotherapy.

Methods

This placebo-controlled, randomized, multicenter, parallel-group phase 2/3 study comprised a screening phase of up to 28 days, an 8-week single-blind prospective treatment phase (Phase A), and a 6-week double-blind, randomized, placebo-controlled treatment phase (Phase B), followed by a 30-day post-treatment observation phase for patients not enrolled in a subsequent long-term extension study (Fig. 1).
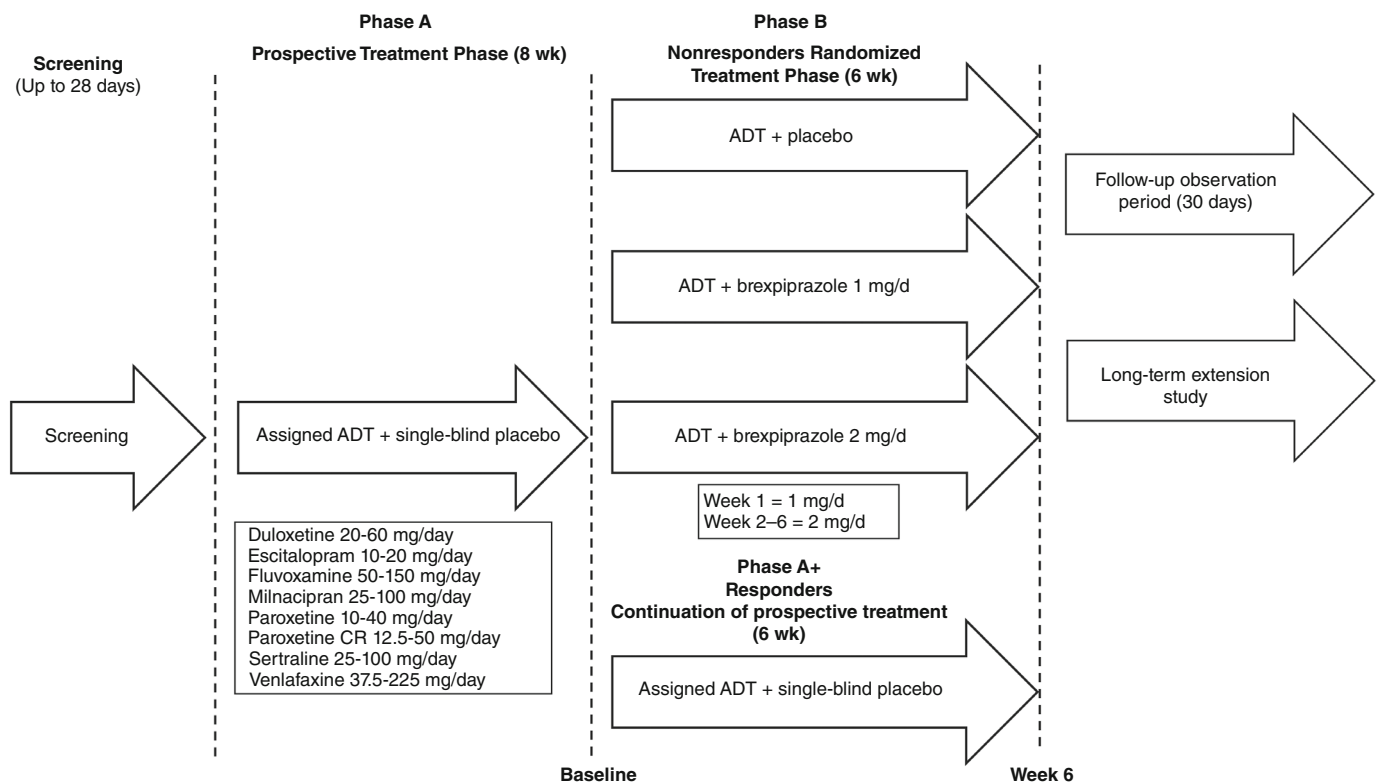
Fig. 1 Study design. Antidepressant responders not meeting the criteria for enrolment in the randomized treatment phase were permitted to continue single-blind antidepressant treatment for an additional 6 weeks at the same regimen and dose as the prospective treatment phase of the study (Phase A+).

The study was approved by the Institutional Review Board (IRB) at the local or central institutional review board at each participating site and complied with Good Clinical Practice (GCP) guidelines, Declaration of Helsinki, and all local laws. All patients provided written informed consent to participate in the study.

This study was registered at ClinicalTrials.gov (NCT03697603).

Patients
Screening eligibility

Japanese adults aged 20 to 64 years were eligible if they had a single or recurrent episode of MDD according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria of ≥8 weeks' duration. Patients were required to be outpatients at the time of informed consent or able to be successfully transferred to outpatient status before enrolment in the antidepressant treatment period (Phase A).

During the current MDD episode, patients were required to have received adequate treatment with 1–3 antidepressants and have had an inadequate response to each agent. Adequate treatment was defined as any antidepressant treatment at an approved dose for ≥6 weeks. Inadequate response was defined as <50% improvement on patient self-evaluation of their previous ADT improvement, with 100% representing complete improvement and 0% representing no improvement in depressive symptoms.

Prospective, single-blind treatment (Phase A) eligibility

Adult outpatients who met screening criteria and had a HAM-D 17-item total score[27] of ≥18 (indicating moderate to severe depression) at screening and initiation of Phase A were eligible for enrolment into the 8-week antidepressant treatment period (Phase A).

Randomized, double-blind treatment (Phase B) eligibility

Patients with a HAM-D 17-item total score of ≥14 (mild to severe depression) at Week 8 of Phase A were subsequently randomized into the double-blind treatment phase (Phase B) if they had an inadequate response to antidepressant treatment, defined as a <50% reduction rate in the HAM-D 17-item total score at Week 8 of Phase A compared with initiation of Phase A, and consistently had a Clinical Global Impression-Improvement (CGI-I) score[28] of between 3 (minimally improved) and 7 (very much worse) throughout Phase A.

Comprehensive inclusion and exclusion criteria are provided in Table S1 and a listing of prohibited concomitant medications is provided in Table S2.

Treatment and randomization

During the prospective treatment phase, patients received placebo in addition to physician-determined treatment with an SSRI or SNRI (Table S3) distinct from the previous antidepressant in a single-blind manner. The antidepressant treatment dose was titrated to within the approved dosage range and then fixed for the last 2 weeks of the 8-week treatment period. Patients were withdrawn if antidepressant treatment was unable to be administered at a fixed dose and regimen for the last 2 weeks of the treatment period for tolerability reasons.

Patients who met the criteria for enrolment in the randomized treatment phase were subsequently randomized in a 1:1:1 ratio to receive double-blind brexpiprazole 1, 2 mg, or placebo once daily for 6 weeks. Both patients and investigators were blinded to treatment during the randomized treatment phase. An interactive web response system was used for assigning treatments using a computer-generated block randomization schedule. The allocation code was not made known to the patient or to the investigator or sub-investigator. For the brexpiprazole 2 mg group, treatment was started at 1 mg once daily until Week 1, then increased to 2 mg once daily until Week 6. The final dosage of SSRI or SNRI used in the prospective phase was continued without any change in dosage or regimen. Study visits took place weekly during double-blind treatment.

Antidepressant responders not meeting the criteria for enrolment in the randomized treatment phase were permitted to continue single-blind antidepressant treatment for an additional 6 weeks at the same regimen and dose as the prospective treatment phase of the study (Phase A+).

Endpoints and assessments

The primary endpoint was the mean change from baseline (Week 8 of Phase A) in MADRS total score at Week 6.[29] Secondary endpoints, assessed at Week 6, included the MADRS response and remission rate, CGI-I improvement rate and mean change from baseline in CGI-S, HAM-D 17-item total scores,[27] mean Sheehan Disability Scale (SDS) scores,[30] and MADRS Self-report (MADRS-S)[31] total scores.

Safety was evaluated by assessment of treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, physical examinations, waist circumference, body weight, body mass index, 12-lead ECG, Columbia Suicide Severity Rating Scale (C-SSRS), drug-induced extrapyramidal symptoms scale (DIEPSS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS).

The incidence and severity of TEAEs (adverse events occurring after initiation of treatment in Phase B) were recorded during each study visit in the double-blind treatment period.

Efficacy and safety-related assessment schedule items have been detailed in Table S4.

Statistical analysis

The sample size calculation was based on an expected effect on the primary efficacy endpoint in the brexpiprazole arms compared with placebo. Based on a previous phase 3 double-blind, placebo-controlled trials of fixed-dose brexpiprazole conducted outside of Japan,[18–20] 654 evaluable patients (218 patients per group) were required to detect with 90% power a between-group difference of −2.4 (SD, 7.7) in mean change from baseline to Week 6 in MADRS total score, at a two-sided significance level of 0.05. Allowing for an attrition rate of 7% due to discontinuations during the double-blind phase and exclusions from the analysis, a total of 720 randomized patients (240 patients per group) were therefore planned.

The full analysis set (FAS), used for all efficacy analyses was defined as all randomized patients who received ≥1 dose of study medication during the double-blind phase and had ≥1 baseline and post-baseline MADRS total score available. The safety analysis set (SAS) used for all safety analyses was defined as all patients who were randomized and received ≥1 dose of study medication during the double-blind phase.

For the primary analysis, a mixed model repeated-measures (MMRM) was fitted with an unstructured variance covariance structure using change from baseline during Phase B in MADRS total score as the dependent variable based on the observed cases dataset. The model included fixed effect terms for treatment group, visit (Weeks 1–6), and interaction between treatment group and visit as factors, and baseline and interaction between baseline and time point as covariates.

For each time point, least square means (LSM) for each treatment group and differences in LSM between each brexpiprazole group and the placebo group, as well as the two-sided 95% CIs were calculated. To control overall type I error rate, a fixed sequence procedure was used. Comparison between brexpiprazole 2 mg and placebo was first performed; comparison between brexpiprazole 1 mg and placebo was performed with a two-sided significance level of 5% only when a statistically significant difference was observed between brexpiprazole 2 mg and placebo at a two-sided significance level of 5%.

For the MADRS response rate, MADRS remission rate, and CGI-I improvement rate, χ^2 tests were performed for between-treatment-group comparisons using the last observation carried

forward (LOCF) data set. CGI-S, SDS, and MADRS-S were analyzed by MMRM in a similar way as for the primary endpoint. For the mean change from baseline in HAM-D 17-item total score, ANCOVA model with treatment group as factor and baseline as covariate was performed using the LOCF dataset. LSM of each treatment group and differences in LSM between each brexpiprazole group and the placebo group, as well as the two-sided 95% CIs were determined.

All statistical analyses were performed using SAS® software version 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 1194 patients were screened from 145 facilities in Japan and were eligible for inclusion in the antidepressant treatment phase (Phase A) (Fig. 2). The trial was held from 30 July 2018 to 4 July 2022. Of these, 1192 patients received antidepressant treatment and 108 patients discontinued treatment during the prospective treatment phase, while 346 patients were considered responders and continued prospective treatment (Phase A+).

A total of 740 patients were eligible for enrolment in the randomized, double-blind treatment phase and received ≥1 dose of brexpiprazole (1 mg, $n = 250$; 2 mg, $n = 246$) or placebo ($n = 244$), which comprised the SAS. Of these, 736 patients (1 mg, $n = 248$; 2 mg, $n = 245$; placebo, $n = 243$) had ≥1 baseline and post-baseline MADRS total score available, which comprised the FAS. Patient disposition is further summarized in Fig. 2. 689 (93.1%) patients completed treatment (brexpiprazole 1 mg, 95.2%; brexpiprazole 2 mg, 89.0%; placebo 95.1%).

Baseline demographics and clinical characteristics were generally similar across treatment groups in the randomized, double-blind phase (Table 1). Mean (SD) MADRS total scores were similar between brexpiprazole 1 mg (26.7 [6.4]), 2 mg (26.9 [6.9]) and placebo groups (27.3 [6.2]) and indicated that patients generally had moderately severe MDD (20–34). For the overall population, the most commonly used concomitant ADT were escitalopram, sertraline, duloxetine, and venlafaxine. Details of assigned concomitant ADT are included in Table S5.

Efficacy
Primary endpoint

In the FAS, the LSM (SE) change from baseline in MADRS total score at Week 6 by MMRM analysis was −8.5 (0.47) in the
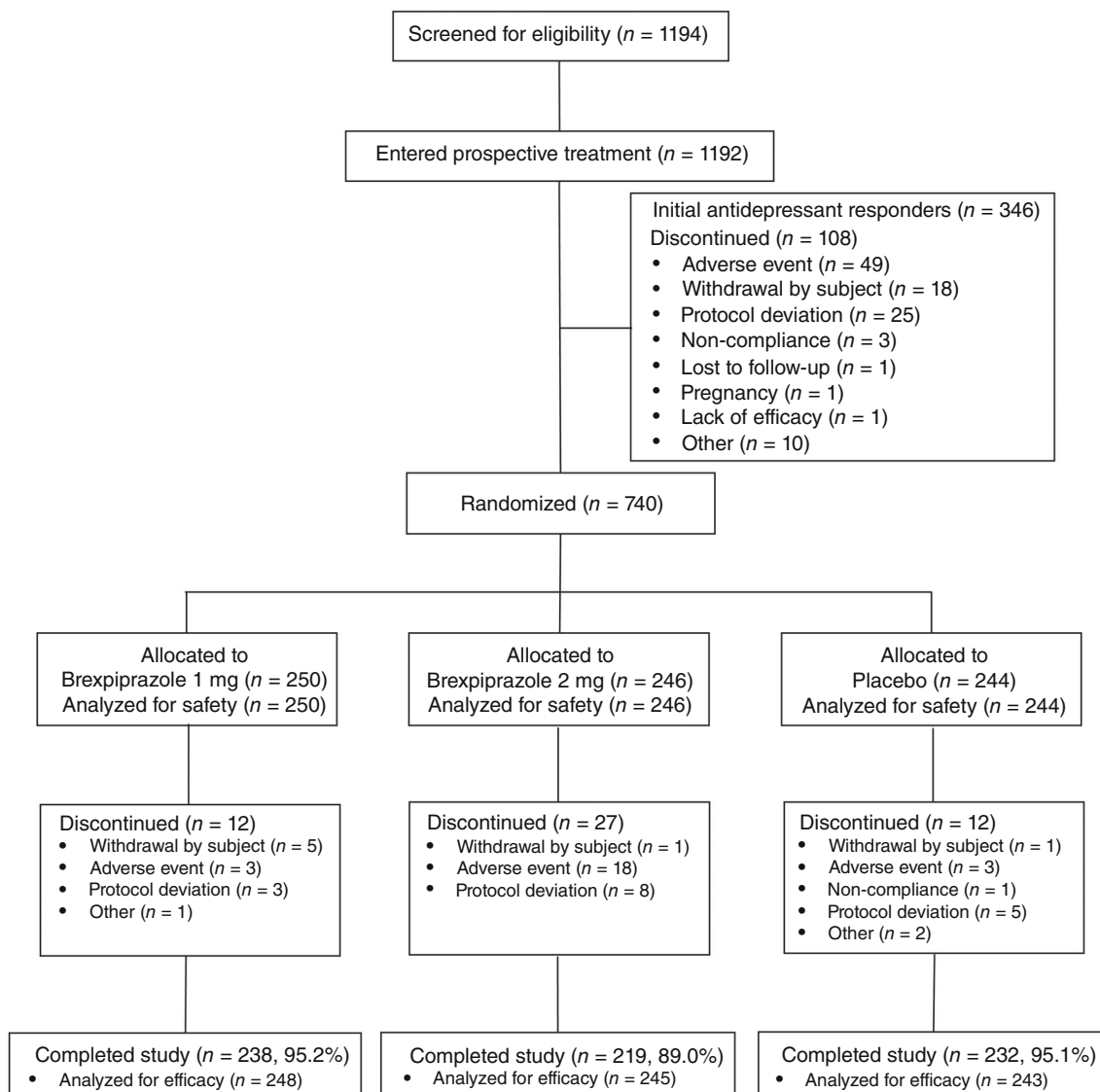
Fig. 2 Patient disposition. Percentages are based on the number of subjects in treatment group; Safety analysis set comprise subjects who have received at least one dose of investigational product in Phase B; Full analysis set comprise subjects who have received at least one dose of investigational product in Phase B, and from whom MADRS total scores have been obtained at baseline and at least one post baseline timepoint.

Table 1. Patient demographics and baseline characteristics (Phase B, FAS)

	Brexpiprazole			
	1 mg ($n = 248$)	2 mg ($n = 245$)	Total ($n = 493$)	Placebo ($n = 243$)
Age, years, mean (SD)	40.9 (10.8)	40.0 (10.7)	40.4 (10.7)	39.8 (10.8)
Sex, male, n (%)	132 (53.2)	143 (58.4)	275 (55.8)	138 (56.8)
BMI, kg/m^2, mean (SD)	23.5 (4.2)	23.8 (4.6)	23.6 (4.4)	23.4 (4.6)
Duration of the current episode (months), mean (SD)	12.2 (16.5)	13.0 (19.1)	12.6 (17.9)	13.5 (22.4)
Number of adequate antidepressant treatments in the current episode, n (%)				
1	191 (77.0)	185 (75.5)	376 (76.3)	189 (77.8)
2	49 (19.8)	48 (19.6)	97 (19.7)	43 (17.7)
3	8 (3.2)	12 (4.9)	20 (4.1)	11 (4.5)
DSM-5 diagnosis, n (%)				
Single episode	95 (38.3)	98 (40.0)	193 (39.1)	91 (37.4)
Recurrent episode	153 (61.7)	147 (60.0)	300 (60.9)	152 (62.6)
MADRS total score, mean (SD)	26.7 (6.4)	26.9 (6.9)	26.8 (6.6)	27.3 (6.2)
HAM-D 17 total score, mean (SD)	20.5 (4.0)	20.8 (3.9)	20.7 (3.9)	21.2 (3.7)
CGI-S score, mean (SD)	4.1 (0.6)	4.2 (0.6)	4.1 (0.6)	4.1 (0.6)

Abbreviations: BMI, body mass index; CGI-S, Clinical Global Impression-Severity of Illness; DSM-5, Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; FAS, full analysis set; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation.

brexpiprazole 1 mg group and − 8.2 (0.47) in the brexpiprazole 2 mg group *versus* −6.7 (0.47) in the placebo group (Table 2, Fig. 3). Placebo-adjusted LSM treatment differences were statistically significant for both brexpiprazole 1 mg (LSM difference [95% CI]: −1.7 [−3.0, −0.4]; $P = 0.0089$) and 2 mg (LSM difference [95% CI]: −1.4 [−2.7, −0.1]; $P = 0.0312$) treatment groups. Improvements in MADRS total score were rapid with both brexpiprazole 1 mg and 2 mg, with separation from placebo observed as early as Week 2 (Fig. 3).

Secondary endpoints

In the FAS, numerical improvements were observed across all secondary endpoints in favor of brexpiprazole 1 mg and 2 mg *versus* placebo (Table 2), supporting the results of the primary endpoint. Brexpiprazole 1 mg showed greater efficacy than placebo ($P < 0.05$) in mean change from baseline at Week 6 in HAM-D 17, SDS and MADRS-S. Brexpiprazole 2 mg showed greater efficacy than placebo ($P < 0.05$) in mean change from baseline at Week 6 in CGI-S and SDS (Table 2). Compared to placebo, brexpiprazole 1 mg did not show significant improvement in MADRS response rate, MADRS remission rate, CGI-I improvement rate and CGI-S at Week 6, while brexpiprazole 2 mg did not show significant improvement in MADRS response rate, MADRS remission rate, CGI-I improvement rate, HAM-D 17 and MADRS-S at Week 6 (Table 2).

Safety

TEAEs, including those with incidence ≥5% in either brexpiprazole group, are summarized in Table 3. TEAEs of any severity grade occurred in 62.0% of patients receiving brexpiprazole 1 mg, 74.0% of patients receiving brexpiprazole 2 mg, and 59.0% of patients receiving placebo. The most common (≥5%) reported TEAEs were weight gain, tremor, akathisia, and nasopharyngitis in the brexpiprazole 1 mg group and akathisia, weight gain, increased serum prolactin level, hyperprolactinemia and nasopharyngitis in the brexpiprazole 2 mg group (Table 3). Most TEAEs were mild or moderate in severity. Severe TEAEs reported by ≥2 patients in either brexpiprazole group were akathisia (1 mg: $n = 1$; 2 mg: $n = 2$; placebo: $n = 0$) and

malaise (1 mg: $n = 0$; 2 mg: $n = 2$, placebo: $n = 0$). TEAEs leading to treatment discontinuation were noted in 0.8% of patients receiving brexpiprazole 1 mg, 7.3% of patients receiving brexpiprazole 2 mg, and 1.2% of patients receiving placebo with akathisia being the most common individual cause for discontinuation (brexpiprazole 2 mg: $n = 6$) and a variety of other causes occurring at low individual rates. In total, eight serious TEAEs were noted during the randomized treatment phase (1 mg: 1.2% [$n = 3$]; 2 mg: 1.2% [$n = 3$]; placebo: 0.8% [$n = 2$]) and constituted the following individual events: appendicitis, intentional overdose, oculomotor nerve paralysis, alcoholic pancreatitis, extramammary Paget's disease, epilepsy, cellulitis, and subarachnoid hemorrhage. However, there were no serious drug-related TEAEs and no deaths occurred in this study. No clinically meaningful changes in laboratory test values, vital signs, or ECG parameters were observed either with brexpiprazole or placebo. When the incidence of TEAEs was examined by CYP2D6 phenotype (IM, EM, PM, Unknown) and by concomitant medication (ADT), there was no significant difference in the incidence of TEAEs in any subgroup, except for some subgroups with fewer subjects. However, plasma brexpiprazole concentrations were higher in IM patients compared to EM patients in all dose groups, except at certain time points.

Aside from akathisia, the rates of activating TEAEs were low overall, including insomnia (1 mg: 3.6%; 2 mg: 4.9%; placebo: 3.3%), restlessness (1 mg: 0.0%; 2 mg: 0.4%; placebo: 0.0%), and anxiety (1 mg: 0.0%; 2 mg: 0.8%; placebo: 0.0%), and occurred at a similar rate to placebo. Extrapyramidal disorder events as a MedDRA preferred term occurred in 4.5% of patients receiving brexpiprazole 2 mg, compared with 0.4% of patients receiving brexpiprazole 1 mg and 0.8% of patients receiving placebo. Most such extrapyramidal disorder events were either mild or moderate in severity. Other subjective negative experiences for patients that have been associated with antipsychotics occurred at a low rate with brexpiprazole, including insomnia, anxiety, and fatigue. Most events of this nature were also mild or moderate in severity, and few cases resulted in discontinuation (e.g., one patient each in the brexpiprazole 2 mg group discontinued due to insomnia or anxiety).

In terms of TEAEs of interest known to be related to antipsychotics, the incidence of extrapyramidal symptom-related TEAEs was

Table 2. Primary and secondary endpoints at Week 6 of the double-blind treatment period (Phase B)

	Brexpiprazole		Placebo (n = 243)
	1 mg (n = 248)	2 mg (n = 245)	
MADRS Total Score, MMRM			
Mean (SD) at baseline	26.7 (6.4)	26.9 (6.9)	27.3 (6.2)
LSM change at Week 6 (SE)	−8.5 (0.47)	−8.2 (0.47)	−6.7 (0.47)
Treatment difference (95% CI)	−1.7 (−3.0, −0.4)	−1.4 (−2.7, −0.1)	
P-value	*0.0089*	*0.0312*	
MADRS Response Rate[†]			
Proportion of responders at Week 6 (LOCF), n (%)	63 (25.4)	60 (24.5)	46 (18.9)
Treatment difference (95% CI)	6.5 (−0.8, 13.8)	5.6 (−1.7, 12.9)	
P-value	*0.0844*	*0.1364*	
MADRS Remission Rate[‡]			
Proportion of patients in remission at Week 6 (LOCF), n (%)	44 (17.7)	43 (17.6)	33 (13.6)
Treatment difference (95% CI)	4.2 (−2.3, 10.6)	4.0 (−2.5, 10.4)	
P-value	*0.2048*	*0.2265*	
CGI-I Improvement Rate[§]			
Proportion of responders at Week 6 (LOCF), n (%)	87 (35.1)	86 (35.1)	72 (29.6)
Treatment difference (95% CI)	5.5 (−2.8, 13.7)	5.5 (−2.8, 13.8)	
P value	*0.1969*	*0.1964*	
CGI-S Score, MMRM			
Mean (SD) at baseline	4.1 (0.6)	4.2 (0.6)	4.1 (0.6)
LSM change at Week 6 (SE)	−0.7 (0.05)	−0.8 (0.05)	−0.6 (0.05)
Treatment difference (95% CI)	−0.1 (−0.3, 0.0)	−0.2 (−0.3, 0.0)	
P-value	*0.0976*	*0.0292*	
HAM-D 17 Total Score, ANCOVA			
Mean (SD) at baseline	20.5 (4.0)[¶]	20.8 (3.9)	21.2 (3.7)
LSM change at Week 6 (SE)	−6.3 (0.34)	−5.6 (0.35)	−5.3 (0.35)
Treatment difference (95% CI)	−1.0 (−2.0, −0.1)	−0.3 (−1.3, 0.6)	
P-value	*0.0330*	*0.4914*	
Mean SDS Score, MMRM			
Mean (SD) at baseline	5.38 (2.16)[††]	5.62 (2.07)[‡‡]	5.62 (2.11)[§§]
LSM change at Week 6 (SE)	−1.13 (0.114)	−1.12 (0.118)	−0.64 (0.115)
Treatment difference (95% CI)	−0.49 (−0.81, −0.17)	−0.48 (−0.80, −0.15)	
P-value	*0.0026*	*0.0038*	
MADRS-S Total Score, MMRM			
Mean (SD) at baseline	10.60 (4.19)	10.90 (4.59)	11.01 (4.28)
LSM change at Week 6 (SE)	−2.46 (0.199)	−1.87 (0.203)	−1.47 (0.200)
Treatment difference (95% CI)	−0.99 (−1.55, −0.44)	−0.41 (−0.97, 0.15)	
P-value	*0.0005*	*0.1543*	

Abbreviations: ANCOVA, analysis of covariance; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity of Illness; CI, confidence interval; HAM-D, Hamilton Rating Scale for Depression; LOCF, last observation carried forward; LSM, least squares mean; MADRS, Montgomery-Åsberg Depression Rating Scale; MADRS-S, MADRS Self-report; MMRM, mixed model repeated-measures; SD, standard deviation; SE, standard error; SDS, Sheehan Disability Scale.

[†]MADRS response rate at Week 6, defined as the proportion of patients with a reduction of ≥50% in MADRS total score from baseline at Week 6.

[‡]MADRS remission rate at Week 6, defined as the proportion of patients with a reduction of ≥50% in MADRS total score from baseline at Week 6 and a MADRS total score of ≤10 at Week 6.

[§]CGI-I improvement rate at Week 6, defined as the proportion of patients with a score of 1 or 2 on the CGI-I scale at Week 6.

[¶]n = 247.

[††]n = 240.

[‡‡]n = 234.

[§§]n = 241.

higher with brexpiprazole (1 mg: 14.8%; 2 mg: 36.6%), compared with placebo (7.4%) although all such symptoms were mild to moderate in severity and no cases of tardive dyskinesia were noted. The LSM (SE) change in DIEPSS total score from baseline to the worst point after administration was 0.4 ± 0.10 with brexpiprazole 1 mg and 1.2 ± 0.10 with brexpiprazole 2 mg. Regarding tardive dyskinesia and akathisia, the AIMS score and the BARS assessment, respectively, showed small changes from baseline to the 6-week evaluation in the 1 mg, 2 mg, and

Table 3. Summary of TEAEs and occurrence of TEAEs with incidence ≥5% in either brexpiprazole group during the double-blind treatment period (SAS)

	Brexpiprazole			Placebo
	1 mg (*n* = 250)	2 mg (*n* = 246)	Total (*n* = 496)	(*n* = 244)
TEAEs	155 (62.0)	182 (74.0)	337 (67.9)	144 (59.0)
Serious TEAEs	3 (1.2)	3 (1.2)	6 (1.2)	2 (0.8)
Severe TEAEs	4 (1.6)	5 (2.0)	9 (1.8)	2 (0.8)
Discontinuation due to TEAEs	2 (0.8)	18 (7.3)	20 (4.0)	3 (1.2)
Deaths	0	0	0	0
Occurrence of TEAEs ≥5% (PT)				
Akathisia	15 (6.0)	60 (24.4)	75 (15.1)	3 (1.2)
Weight increased	18 (7.2)	19 (7.7)	37 (7.5)	6 (2.5)
Nasopharyngitis	20 (8.0)	16 (6.5)	36 (7.3)	24 (9.8)
Tremor	16 (6.4)	12 (4.9)	28 (5.6)	9 (3.7)
Blood prolactin increased	6 (2.4)	15 (6.1)	21 (4.2)	6 (2.5)
Hyperprolactinemia	3 (1.2)	13 (5.3)	16 (3.2)	3 (1.2)

Note: Data are presented as *n* (%).
Abbreviations: PT, preferred term; TEAE, treatment-emergent adverse event.

placebo groups and no clinically meaningful changes were observed. Prolactin levels increased from baseline at final assessment with brexpiprazole but remained within the reference range at this point for both men and women. As noted previously, weight gain was greater among patients treated with brexpiprazole but all events were mild or moderate in severity and none led to treatment discontinuation.

Regarding the time of onset of TEAEs, the greatest single proportion of events in each group occurred in between day 1 and day 7 of treatment (1 mg: 22.0%; 2 mg: 27.2%; placebo: 23.0%) with no events having a higher incidence with increasing duration of treatment. Further, there were no significant differences in the incidence of TEAEs by time of first onset between the brexpiprazole and placebo groups.

In terms of C-SSRS results, no suicidal behavior was observed at baseline while one patient in the brexpiprazole 2 mg group exhibited suicidal behavior after administration. After administration of treatment, the rate of suicidal ideation was 15.2% of patients in the brexpiprazole 1 mg group, 19.5% of patients in the brexpiprazole 2 mg group and 17.6% of patients in the placebo group.

Discussion

This placebo-controlled, randomized, phase 2/3 study is the first to comprehensively evaluate the efficacy and tolerability of brexpiprazole as adjunctive therapy in Japanese patients with MDD who showed an inadequate response to antidepressant monotherapy. Improvements in patients receiving adjunct brexpiprazole were greater than in patients taking adjunct placebo, as shown by statistically significant differences *versus* placebo in the primary endpoint of change from baseline in MADRS total score at week 6 for both brexpiprazole 1 mg and 2 mg. Numerical improvements in secondary endpoints in favor of brexpiprazole 1 mg and 2 mg *versus* placebo reflected the results of the primary endpoint. Overall, TEAEs were common in all
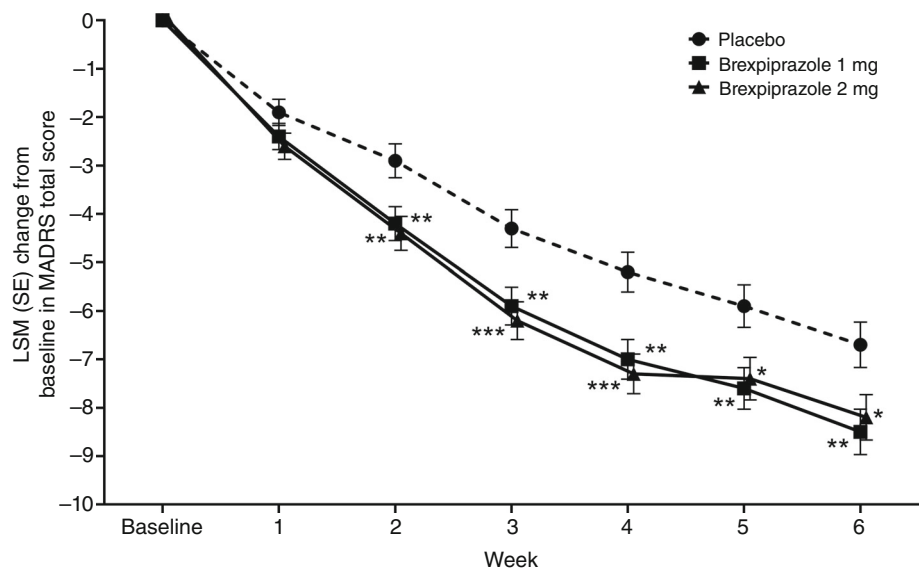
Fig. 3 LSM (SE) change from baseline in MADRS total score by MMRM analysis (FAS population). *P < 0.05; **P < 0.01; ***P < 0.001.

	Baseline	1	2	3	4	5	6
Placebo	243	243	233	237	232	231	233
Brexpiprazole 1 mg	248	248	240	237	233	233	237
Brexpiprazole 2 mg	245	244	238	231	226	223	218

treatment groups, but there were few serious TEAEs. The incidence of certain TEAEs, including akathisia and elevated serum prolactin levels, tended to be higher in patients who received brexpiprazole 2 mg. However, most TEAEs were mild or moderate in severity. The most common TEAEs associated with brexpiprazole were akathisia, weight gain, nasopharyngitis, tremor, increased serum prolactin level, and hyperprolactinemia. There were no notable differences in the incidence of TEAEs by first onset between brexpiprazole and placebo. As such, there is no suggestion that the incidence of tolerability issues increases over time with brexpiprazole.

Efficacy results in the present study are generally consistent with those reported in similar international phase 3 trials of brexpiprazole for this indication.[18–20] Baseline depression scores in the present study were similar to those in pivotal overseas trials among non-Japanese patients. It should be noted that the primary endpoint was not achieved with brexpiprazole 1 mg in these overseas trials but, for the first time, was achieved among Japanese patients in this study. Given current prescribing patterns in Japan for MDD, it is also worthwhile to compare these results with those of the ADMIRE study, which was designed to evaluate the efficacy and safety of adjunctive aripiprazole in Japanese patients with MDD.[12] Although it is not possible to make an unambiguous comparison due to differences in patient backgrounds and the time of the trial, the design, patient population, and inclusion criteria of the current study and ADMIRE are sufficiently similar to allow such comparisons. Briefly, patients in the 3-arm ADMIRE study were randomized to adjunctive aripiprazole either as a fixed 3 mg daily dose or a flexible 3–15 mg daily dose or to placebo and were studied over 6 weeks, with an identical primary endpoint as the current study. Change in mean MADRS total score for the adjunctive fixed dose or flexible dose of aripiprazole were significantly greater than with adjunctive placebo. The differences in mean MADRS total score *versus* placebo are −2.2 to −3.1 with aripiprazole in the ADMIRE study compared with −1.4 to −1.7 in the current trial. However, some of this difference between aripiprazole and brexpiprazole may relate to differences in patient background. For example, the proportion of patients with recurrent episodes at baseline in the BLESS study (60.0–62.6%) was notably higher than in the ADMIRE study (38.1–47.4%) and recurrent episodes have been identified as more difficult to treat.[32] In Japanese patients, it appears that, brexpiprazole 1 mg is an appropriate starting dose at which the primary endpoint was met thus also making it an effective target dose. Further, 1 mg may also avoid the increased tolerability issues associated with 2 mg. As mentioned above, this represents one of the key novel features of this study.

In terms of tolerability, results of the present study were generally consistent with those of international trials with various points of difference in terms of incidence. In international trials, the incidence of akathisia with brexpiprazole 1 mg (4.4%) and 2 mg (7.4–8.3%) were lower than in patients who received brexpiprazole 1 mg (6.0%) but especially those who received 2 mg (24.4%) in this study. The incidence of akathisia with aripiprazole observed in the ADMIRE study was notably higher than in the present study, especially with the flexible dosing strategy (36.6% for aripiprazole 3–15 mg *versus* 4.1% for placebo) but also with the fixed dosing strategy (14.2% for aripiprazole 3 mg *versus* 4.1% for placebo). Although there was no detected bias in patient background factors related to akathisia among the studies,[33] the pathophysiology of akathisia is poorly understood. However, as mentioned previously, a relatively lower level of intrinsic activity at D_2 receptors and more potent actions at $5HT_{1A/2A}$, than aripiprazole may underlie the lower rates of akathisia as well as agitation and activating symptoms noted in relevant clinical trials.[15] It should be reinforced that most cases of akathisia in the present study were mild or moderate in severity and severe cases were reported in only one patient in the brexpiprazole 1 mg group and two patients in the brexpiprazole 2 mg group (*versus* no patients in the placebo group). The discontinuation rate from akathisia among patients who received brexpiprazole 2 mg was approximately 2.4% compared with 0.0% among patients who received brexpiprazole 1 mg or placebo.

Further, most cases of akathisia resolved either following treatment or upon discontinuation. Results of assessments such as BARS showed small changes from baseline to the final evaluation in all treatment groups, with no clinically meaningful changes at the final assessment.

The apparent large increase in the incidence of akathisia between 1 mg and 2 mg in the present study also deserves more detailed discussion. In international trials, the incidence of akathisia across the range of 1–3 mg daily has been noted to show a monotonic increasing trend,[34] whereas the incidence in Japanese patients treated with 2 mg seems to deviate from this trend. The lack of apparent difference in BARS scores should be considered in light of the fact that this was only assessed at two observation points, which may be insufficient to detect changes occurring during treatment. Some CYP2D6 phenotypes and the type of concomitant ADT used may have an effect on brexpiprazole blood levels and the CYP2D6*10 allele has also been suggested as a risk factor for extrapyramidal symptoms, including akathisia, in Asian patients with mood disorders.[35,36] However, the incidence of AEs examined by CYP2D6 phenotype (IM, EM, PM, Unknown) and by concomitant medication (ADT) showed there were no significant differences, except for some subgroups with fewer patients. This suggests that these genetic factors did not affect akathisia incidence in this study. Differences in pharmacokinetics and pharmacodynamics of brexpiprazole due to possible impact of gene variability requires further exploration. Unfortunately, however, data on the impact of genetic variations on brexpiprazole pharmacodynamics and tolerability are still limited.[37]

Despite their widespread use, attention to potential tolerability issues other than akathisia is important when considering using antipsychotic medication in patients with MDD.[38] Extrapyramidal symptoms, metabolic syndrome effects, increased prolactin levels, and subjective negative experiences such as insomnia are particularly important to consider. A systematic review and meta-analysis of antipsychotics found that brexpiprazole provided a favorable number-needed-to-harm (NNH) value compared with antipsychotics overall (NNH: brexpiprazole, 57; overall, 37).[9] Further, NNH values associated with brexpiprazole for weight gain (NNH = 20) and akathisia (NNH = 17) were more favorable than certain other antipsychotics with available data (NNH for weight gain for olanzapaine, 9; akathisia for aripiprazole, 7).[9] Results from our study found that the incidence of insomnia, which represents a key activating TEAE of brexpiprazole, was relatively similar compared with international trials. Considering the differences with the placebo group, the incidence of insomnia was lower with brexpiprazole in the current trial than with aripiprazole in the ADMIRE study. Weight gain also occurred at a similar rate in both Japanese and non-Japanese patients although incidences were consistently higher in placebo-treated patients in both populations. A recent large international preference study identified insomnia, anxiety, and fatigue as the most important non-serious AEs troubling to patients treated for depression.[13] The fact that the incidence of these specific AEs was relatively low in the present trial is reassuring.

Limitations of the current study are similar to those of previous studies of brexpiprazole for this indication and are mainly the short treatment duration and lack of an active comparator. Regarding this, a long-term extension of this study was conducted (NCT03737474) and will be published separately. The generalizability of this study is also limited to Japanese patients and with respect to the eligibility criteria. However, given the primary purpose of this study in evaluating the efficacy and tolerability of brexpiprazole specifically among Japanese patients with MDD and inadequate response to antidepressant therapy, this should not be viewed as a notable limitation. Notwithstanding this, further studies, including real-world studies and comparative studies among Japanese patients would provide useful additional information for clinicians.

Conclusion

Results of this study found that brexpiprazole 1 mg daily was an appropriate starting dose and brexpiprazole 1 mg and 2 mg daily were

effective and well tolerated as adjunctive therapy for Japanese patients with MDD not adequately responsive to ADT monotherapy.

Author contributions

Acknowledgements

Disclosure statement

Data availability statement

Anonymized individual participant data that underlie the results of this study will be shared with researchers to achieve aims prespecified in a methodologically sound research proposal.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section at the end of this article.